REMARKS

The November 22, 2010 Official Action and the references cited therein have been carefully considered. In view of the amendments submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the Official Action. The initial due date for response, therefore, was February 22, 2011. A petition for a two (2) month extension of the response period is included with this amendment and request for reconsideration, which is being filed before the expiration of the one (2) month extension period.

Turning to the substantive aspects of the November 22, 2010 Official Action, the Examiner has objected to claim 55 for containing a minor informality. The word "and" has been inserted into the claim before the term "S435", thereby rendering this objection moot.

The Examiner has rejected claims 22, 26, 32, 36, 38, 39, and 55 under 35 USC §103(a) as allegedly unpatentable over US Patent 5,994,084 to Anderton, in view of Singh1, Singh2, Graves, US Patent 6,593,512 to Vitek and Litersky.

Claims 22, 26, 27, 32, 36, 38, 39, and 55 stand rejected under 35 USC §103(a) as allegedly unpatentable over the '084 patent to Anderton in view of Lau et al., Graves, Vitek, Hasegawa and Yamamoto.

At page 12 of the Official Action, the Examiner has newly rejected claim 27 as allegedly obvious over the '084 patent to Anderton, Singh1, Singh2, Graves, Vitek and Litersky and further in view of Hasegawa.

Claims 41 and 42 are also newly rejected as allegedly obvious over the combination of US Patent 5,994,084 to Anderton, in view of Singh1, Singh2, Graves, US Patent 6,593,512 to Vitek and Litersky or US Patent 5,994,084 to Anderton, Lau, Graves, US Patent 6,593,512 to Vitek Hasegawa, Yamamoto and further in view of Zhu.

The Examiner has formulated new rejections of claim 22, 26, 32, 36, 38, 39, 41, 42 and 55 based on obviousness-type double patenting

The foregoing objections and rejections constitute all of the grounds set forth in the November 22, 2010 Official Action for refusing the present application. For the reasons given below, each of these grounds of rejection are respectfully traversed.

INTRODUCTION

Applicants have identified phosphorylation sites on tau that are associated with Alzheimer's Disease and have identified CK1 as being responsible for this specific phosphorylation. This finding gave rise to the instantly claimed method to more accurately predict therapeutically efficacious inhibitors of CK1. The problem was solved, in accordance with the present invention, through the provision of a number of previously un-described, phosphorylation sites in tau protein that are found in pathological forms of PHF tau, but which are not found to be phosphorylated in normal tau, and means for quantifying the level of phosphorylation at each site. The sites set forth in the amended claims were not described or suggested in the prior art. See, in particular, claims 32 and 55.

At the outset, Applicants are dismayed that the Examiner has once again rejected the claims based on obviousness citing prior art that fails to place the method presently claimed in the possession of the public. The Examiner is once again reminded that silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow. In re Burt, 148 U.S.P.Q. 548 (CCPA 1966). Applicants reiterate that with respect to all of the prior art rejections and obviousness-type double patenting rejections, many of the predetermined sites on tau phosphorylated by CK1 in the pending claims were unknown prior to the present invention as was their association with pathological forms of tau. Notably, the claims have been amended to require detection of these novel phosphorylation sites, rather than all and any phosphorylation sites on tau that may or may not be associated with disease.

Applicants had been under the impression that the amendments to claim 22 placed the application in condition for allowance. Prior to submission of the Request for Continued Examination, a draft claim 22 was sent to the Examiner for his consideration. On January 5th, 2010, Examiner Steadman suggested further amendments which were discussed in a telephonic interview which was held on January 7th, 2010 between Examiner Steadman, the undersigned and Dr. Ian Pike. In response to the Interview, Applicants submitted an RCE which resulted in the issuance of the Official Action of November 22. In this Official Action, the Examiner withdrew his previous rejections based on obviousness in favor of new rejections relying on a subset of the 13 references previously cited. As in the previous Official Actions, Applicants once again submit that a prima facie case of obviousness has not been established and further

that the present method represents an advance in the art of identifying efficacious agents for the treatment of Alzheimer's Disease. As such, it is deserving of patent protection. Applicants also note that each of the "new rejections" could have been raised earlier in prosecution as the amendments presented did not materially alter the scope of the claims. Moreover, the prior art, as reflected in cited references considered in combination fails to provide the factual underpinning to support a finding that the presently claimed screened method is prima facie obvious. The present invention can hardly be considered a combination of prior art elements according to known methods to yield predictable results. As the following discussion will clearly demonstrate, at the time the present invention was made predictably with respect to tau phosphorylation was woefully lacking.

CLAIMS 22, 26, 32, 36, 38, 39, AND 55 AS AMENDED ARE PATENTABLE OVER THE PRIOR ART CITED BY THE EXAMINER

A1. The aforementioned claims stand newly rejected under 35 U.S.C. §103 as allegedly obvious over the '084 patent to Anderton in view of Singh1, Singh2, Graves, US Patent 6,593,512 to Vitek and Litersky.

Claim 22 as amended specifically identifies a select number of sites rather than "any and all phosphorylation sites" present on the tau protein and requires that a single enzyme, CK1 or a closely related variant thereof phosphorylate tau at one or more of these sites. Citing references which merely indicate that isolated elements in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been *prima facie* obvious. *Ex parte Hiyamizu,* 10 USPQ 1393, 1394 (PTO BPAI 1988). To the same effect is *Ex parte Levengood,* 28 USPQ 1300 (PTO BPAI 1993) (examiner cannot establish obviousness by locating references which describe various aspects of applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what applicant has done). Here, as in *Levengood,* the references cited as evidence of obviousness "fall short of providing the 'motivation' or 'suggestion' to assemble their teachings into a viable process". *Id.* at 1302.

The Examiner relies on the '084 patent to Anderton for teaching a cell based system for studying tau phosphorylation. However, the '084 patent is concerned with analysis of the actions of mitogen activated kinases and their ability to phosphorylate tau. Specifically, Anderton et al.

disclose at column 4:

"Such in vitro studies have revealed that mitogen activated kinases (also known as microtubule-associated kinases and abbreviated herein to "MAP" kinases), for example, p42 MAP kinase, and also glycogen synthase kinase 3 alpha and 3 beta (GSK-3α. and GSK-3β), cdc2 kinase, cdK5 kinase and one or more brain proline-directed kinases are capable of phosphorylating tau on at least some residues which are phosphorylated in PHF-tau (Biernat et al., 1992; Drewes et al., 1992; Gustke et al., 1992; Hanger et al., 1992; Ishiguro et al., 1992; Ledesma et al., 1992; Lichtenberg Kraag et al., 1992; Mandelkow et al., 1992; Vulliet et al., 1992). All of the above kinases are therefore candidates for modulating the phosphorylation status of tau in vivo."

Notably, CKI is not listed anywhere in the '084 patent. Moreover CK1 is not a "proline directed" kinase. Finally, the antibodies disclosed in the patent will not unambiguously identify all phosphorylated sites on tau listed in claim 22.

Applicants agree with the Examiner's assertion that Anderton does not teach or suggest using a combination of CK1 and CaM kinase II. The only kinases Anderton suggests using in combination in the disclosed system are the MAP kinases listed above.

Singh et al. (Singh 1) describes a very low resolution analysis of tau phosphorylation by a range of kinases. They show that casein kinase 1 is one of six protein kinases able to phosphorylate tau *in vitro.* CK1 was also shown to have the highest activity of the six kinases tested. Using antibodies Tau-1 and 102c they confirm that the sites of the epitopes recognized by these antibodies are not phosphorylated. Thus, ser 199 and ser 202 are not phosphorylated by any of the six kinases studied. In fact, Singh et al. do not provide any site specific information for CK1 phosphorylation of tau protein. In figure 5 they show that patterns of ^{32}P incorporation into chymotrypsin digests of tau by different kinases have several similarities and some differences. However, they do not state any specific sites that are phosphorylated by CK1 either alone or in combination.

In the discussion, Singh1 reports that phosphate incorporation of tau was highest when CK1 and CaMKII were used in combination. Thus Singh 1 provides no teaching as to which sites in tau are phosphorylated by CK1. Singh 1 therefore provides no more than an invitation to experiment with no prediction of the likelihood of success to arrive at the present invention. The last page of Singh 1 admits as much, starting at page 187 last line over to page 188, "The participation of one or more of the non-PDPKs (CK1, CK2, A kinase, C-Kinase, CaM kinase II,

Gr kinase) in the in vivo phosphorylation of tau still needs to be clarified. Indeed, the authors conclude with the following statement "The sites in tau phosphorylated by CK1 and Gr kinase are still to be identified and compared to those phosphorylated in PHF tau".

Singh2 likewise, does not disclose the predetermined sites on tau that are phosphorylated by CK1 solely. These investigators were concerned with how the specificity of a non-PDPK for different sites on human tau 39 is modulated when tau is prephosphorylated by other non-PDPKS as a well as a PDPK. As with the '084 patent to Anderton, the antibodies disclosed in the Singh references will not successfully identify all of the phosphorylated residues in tau currently listed in claim 22. At page 148 of Singh2, these investigators disclose "The results presented in this study are part of our continuing efforts to decipher the roles of non-PDPKs in tau hyperphosphorylation" At page 149, Singh2 teach that when acting alone, these kinases induce an Alzheimer's like state in tau only slowly and that prephosphorylation by another kinase can increase this rate. Moreover, Singh2 is unclear as to whether CK1 is acting to directly phosphorylate tau at thr 231, ser 396 and ser 404, but rather hypothesize it may be phosphorylating other proline independent sites which can induce a conformation change which in turn modifies the bonding the SM131, SM134 and M4 antibodies. Finally as in all the references discussed above, this reference fails to teach or suggest the Markush group of sites recited in claim 22.

According to the Examiner, Singh1 teaches the possibility of using these two kinases together because when tested in concert they phosphorylate tau to higher stoichiometries relative to use of a single kinase. Singh2 is relied on for the teaching that tau can be converted to an Alzheimer like state after phosphorylation by CK1 and that sites of CK1 phosphorylation in PHF-tau were phosphorylated more rapidly and to a greater extent if tau is prephosphorylated by CaM kinase II. The fundamental deficiencies of the Singh references are discussed above. Applicants are confounded by the Examiner's rationale in making this argument. First, the instant method is testing the ability of a candidate substance to interfere with **CK1 kinase** action at predetermined sites on tau. The skilled person would not be motivated to utilize another kinase in this assay method as this would skew the interpretation of the data. Moreover, Singh et al. is not at all certain that CK1 is phosphorylating the sites in question. See page 149.

There is no apparent reason for combining Graves with the '084 patent and Singh1 and Singh 2. Applicants do not dispute that Graves discloses a cDNA encoding a 428 amino acid

polypeptide, designated CK1δ, which is identical to that presently recited in claim 22. However, one searches Graves in vain for any disclosure or suggestion of a practical utility for the CK1δ described therein.

Vitek provides no teaching or suggestion of using human tau protein produced by the transgenic mouse disclosed therein in a screening assay for inhibitors of any kinase, much less CK1 inhibitors. Vitek is concerned solely with a transgenic mouse, which expresses the human tau gene, and which is disclosed as being useful as a source of human tau protein and as a model of Alzheimer's disease, Frontal Tempral Dementia and Parkinson's-like diseases.

The Examiner relies on Litersky for the teaching that tau is phosphorylated at S416 by CaM kinase II and states that a priori knowledge that CK1 phosphorylate S416 is not required. Applicants respectfully disagree. First, Applicants method does not read on the use of a combination of kinases. Indeed, this is the subject matter of the invention withdrawn from consideration. See claim 33 for example. Second, the claim requires that CK1 be able to phosphorylate tau at one or more predetermined sites, the recited sites including S416. Third, the term CK1 does not appear in Litersky. Fourth, the observation that CAMKII and cAMP-PK act to phosphorylate tau provides no motivation or incentive whatsoever for the skilled artisan to use CK1 for this purpose. Again, Applicants submit that the skilled person would not be motivated to use a combination of kinases as suggested by the Examiner. Additionally, none of these references when considered alone or in combination disclose each and every element of the present method. Indeed, Litersky concludes with the following statement: "Whether phosphorylation at Ser262 and Ser 356 is achieved by cAMP-PK, CaMKII or the recently described p110^{mark}, or by some combination of these, or other undescribed kinases will be an important question in Alzheimer's disease research."

The rationale given by the examiner for combining these particular groups of references in support of these rejections is dubious at best. The cited references make clear that the exact role of any candidate tau kinase in Alzheimer's disease "is an important question in Alzheimer's disease research (Litersky et al. at page 660) and that the sites phosphorylated by CK1 on tau "remain to be identified". (Singh1, page 188). Anderton et al. and Litersky are not at all concerned with CK1 kinase action on tau and the addition of Singh1 and Sing2, Graves and Vitek do nothing more that offer the skilled person an invitation to experiment to arrive at what Applicants have done. Applicants are not employing a "combination of kinases" as asserted by

the Examiner at page 8 and thus the activity of CaM kinase II against tau does not render the presently claimed method obvious in any way. It is submitted that these disclosures fail to place each and every element of the method of claim 22 as amended in the hands of the public. Accordingly, a prima facie case of obviousness has not been established. Thus the rejection of claims 22, 26, 32, 36, 38, 39, and 55 on this ground is untenable and should be withdrawn.

B1. Claims 22, 26, 27, 32, 36, 38, 39, and 55 stand newly rejected over the '084 patent to Anderton in view of Lau et al., Graves, Vitek, Hasegawa and Yamamoto. As in the rejection above, the Examiner relies on the '084 patent to Anderton as the primary reference. Again, the skilled person having the Anderton et al. patent before him or her would be motivated to study the action of MAP kinases on tau. There is simply no motivation to be gleaned from Anderton relating to testing any and all possible kinases that may or may not phosphorylate tau.

Lau et al. disclose in the abstract that the key challenges in developing effective therapeutic agents include "identification of the relevant kinases responsible for aberrant tau phosphorylation in AD, synthesis of inhibitors selectively targeting those kinases and establishment of proper animal models" . Lau also teaches at the top of page 399 that twenty five phosphorylation sites have been identified on tau. Notably, the present inventors provide 32 sites on tau which are phosphorylated by CK1. Lau also notes that many different kinases exhibit activity against tau and lists no less than 10 kinases which exhibit the capacity to phosphorylate tau. Moreover, the identity of the kinases actually responsible for the Alzheimer's phenotype remains an open question as evidenced by the following statement at page 399, lines 12-16: "The conviction of any one of these suspect kinases as guilty parties in mediating tau pathology will depend upon the development of highly specific inhibitors that are efficacious in reducing tau pathology in animal models and, ultimately, in AD patients" Such statements in the references cited in support of the present rejections clearly render the examiner's certainty in asserting that CK1 was a valid therapeutic target rather presumptuous.

As above, the addition of Graves and Vitek to this rejection amount to no more than an identification of references that disclose isolated elements of instant method. Certainly the skilled person considering the '084 patent in combination with Lau, Graves and Vitek would not arrive at the method encompassed by the claims.

Yamamoto is relied on for teaching the use of mass spectrometry for identifying

phosphorylation sites on tau. Applicants note that Yamamoto et al. is exclusively concerned with CaM Kinase II phosphorylation of bovine tau. Using a LC/MS approach they identified five phosphopeptides in a tau protein digest and defined two sites, namely serine 262 and serine 356. The other sites could not be precisely defined. At no point does Yamamoto et al. mention Casein Kinase I as a candidate tau kinase despite a detailed analysis of other kinases (PKA, PKC) in the discussion. Furthermore, Yamamoto concludes that "As PHF-tau was Phosphorylated at serines 262 and 356 but not serine 324, it may well be that CaM Kinase II is the most likely candidate for involvement in hyperphosphorylation of PHF-tau among these protein kinases. Thus, the skilled artisan would not be motivated to consider other candidate kinases as being responsible for phosphorylation at these sites. Moreover, this reference still does not disclose the thirty two discrete sites which are capable of being phosphorylated by CK1 despite the Examiner's contention that the methodology disclosed makes such determinations possible. The Examiner is reminded that these kinases do not phosphorylate tau in an identical fashion. Indeed, at page 17052, Yamamoto teach that Thr-231 was "unambiguously identified as an "abnormal phosphorylation site". Notably, this site is not phosphorylated by CK1 and is absent from the present claims.

Hasegawa is also relied on for teaching that tau phosphorylation can be assessed using mass spectrometry. Applicants do not dispute that mass spectroscopy is useful for identifying and characterizing post translational modifications of proteins. However, despite the availability of this method, the phosphorylation sites on tau associated with CK1 activity and Alzheimers disease were not recognized until Applicant's invention. As with the rejection based on obviousness above, the disclosures in the cited references provide nothing more than an invitation to experiment. They fail to unambiguously disclose that which applicants have done. In view of the foregoing, it is clear that the present rejection relies on impermissible hindsight, is improper and should be withdrawn.

C1. Claim 27 stands newly rejected as allegedly obvious over the '084 patent to Anderton in view of Singh1, Singh2, Graves, US Patent 6,593,512 to Vitek, Litersky and further in view of Hasegawa. Applicants submit that as in the aforementioned rejections, the Examiner has failed to establish a prima facie case of obviousness. The deficiencies in the combination of the '084 patent to Anderton in view of Singh1, Singh2, Graves, US Patent 6,593,512 to Vitek and

Litersky have been discussed at length above. The combination of these references does not render the presently claimed method prima facie obvious and merely comprises an invitation to the skilled artisan to experiment. Hasegawa does not compensate for this deficiency in a meaningful way. Applicants submit that a tau protein missing a single amino acid at the N terminus would not be considered a "fragment" of tau as contemplated by claim 27. However, even if the tau of Hasegawa were considered to be a fragment, Hasegawa with the necessary tools according to the Examiner was still unable to identify the relevant sites on tau phosphorylated by CK1. Nor can the motivation to do so be gleaned from this reference. The conclusion is inescapable, therefore, that applicants' improved method of identifying specific inhibitors of CK1-mediated phosphorylation at specific sites on tau protein is patentably distinguishable over the references of record.

D1. The Examiner has rejected claims 41 and 42 as allegedly unpatentable over the combination of US Patent 5,994,084 to Anderton, in view of Singh1 Singh2, Graves, US Patent 6,593,512 to Vitek and Litersky or US Patent 5,994,084 to Anderton, Lau, Graves, US Patent 6,593,512 to Vitek, Hasegawa, Yamamoto and further in view of Zhu. As set forth above in Section A of this response, the first combination of references does not render the instant claims obvious. It is axiomatic that if the independent claim is not rendered obvious by a combination of references, the dependent claims cannot be held obvious. The content of each of these references and their deficiencies when considered alone or in combination has been addressed in detail above with the exception of Zhu. Zhu et al. teaches the use of protein chips for protein kinase assays. While Zhu contemplates coupling protein arrays with mass-spectrometric analysis in drug discovery, the reference provides no teaching or suggestion of the use of mass spectrometry to measure specific tau phosphorylation sites to determine whether an inhibitor has prevented phosphorylation by CK1. Once again, it is submitted that the references relied on by the Examiner fail to place each and every element of the method of claims 41 and 42 in the hands of the public. Accordingly, a prima facie case of obviousness has not been established and thus the rejection of claims 41 and 42 on this ground is untenable and should be withdrawn.

CLAIMS 22, 26, 27, 32, 36 38, 39, 41, 42 AND 55 ARE PATENTABLY DISTINCT OVER CLAIMS 6-9 AND 12 OF US PATENT 5,994,084 TO ANDERTON ET AL. IN VIEW OF SINGH3, GRAVES, VITEK, HASEGAWA AND YAMAMOTO

A2. Obviousness-type double patenting is a judge-made doctrine based on public policy, which has as its objective the prevention of unjustified or improper time-wise extension of the right to exclude conferred by a U.S. patent. This policy is effectuated by refusing issuance of separate patents on applications that claim obvious variations of the same invention. In this case, however, there is no possibility for unjustified or improper time-wise extension of applicants' patent rights because the present claims cannot possibly constitute an obviousness variation of the method for testing therapeutic agents for treating Alzheimer's disease claimed in claims 6-9 and 12 of the '084 patent.

The impropriety of the present rejection has been addressed at length in applicant's previous responses. Claim 22 does not read on "necessarily analyzing any and all sites of phosphorylation of tau". Rather claim 22 is directed at identifying inhibitors which interfere with CK1 phosphorylation of tau at 32 distinct sites, several of which were unknown to be associated with Alzheimer's disease until Applicants filing of this application. It is clear that the disclosure in the '084 patent fails to place the method of claim 22 as amended in the possession of the public. Nor would the skilled person having the '084 disclosure before him or her arrive at the subject matter instantly claimed. Again, the Examiner is stressing the lack of teaching of a combination of kinases comprising GSK-3 and CK1 in the Anderton patent. Applicants assay method is based on determining the actions of a single kinase, CK1 on tau hyperphosphorylation that had previously been associated with Alzheimer's pathology. The addition of Singh3, Graves, Vitek, Hasagawa and Yamamoto fail to support the Examiner's position. Indeed, Singh3 who were studying the in vitro phosphorylation of tau by a variety of kinases concludes with the following paragraph:

"Tau has been shown to be a substrate for seven non-PDPKs. These include the six kinases studied here (A-kinase, C-kinase, CK-1, CK-2, CaM kinase II and Gr kinase). How many of these seven kinases actually do participate in the hyperphosphorylation of PHF-tau **is still unknown.** ....The finding that a casein kinase (which has several CK-1 like properties) is associated with PHFs further supports this hypothesis. **Identification of the sites phosphorylated in tau by CK1 should clarify this issue."**

As discussed at length above, the cited references alone or in combination do not provide the necessary factual foundation to support a rejection based on obviousness-type double patenting. Accordingly, the rejection is without merit and should be withdrawn.

B2. Claims 41 and 42 have been rejected under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claim 6 of the '084 patent to Anderton in view of the teachings of Singh3, Graves, Vitek, Hasegawa, and Yamamoto and further in view of Zhu. The inadequacy of this combination of references has been discussed above, particularly in sections A1 and D1 above. It is readily apparent that the presently claimed method is patentably distinct from the method claimed in the '084 patent, and the added disclosures of Singh3, Graves, Vitek, Hasagawa, Yamamoto and Zhu do not supply the noted deficiencies in this patent.

CONCLUSION

It is respectfully requested that the amendment presented herewith be entered in this application, since the amendment is primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

In view of the amendment presented herewith, and the foregoing remarks, it is respectfully urged that the rejections set forth in the November 22, 2010 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone or in-person interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
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